Long-term Outcomes of Follow-up for Initially Localised Clear Cell Renal Cell Carcinoma: RECUR Database Analysis

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Abstract

Background: Optimal follow-up (FU) strategy to detect potentially curable (PC) recurrences after treatment of localised clear cell renal cell carcinoma (ccRCC) is unclear. This study retrospectively analysed a large international database to determine recurrence patterns and overall survival (OS), as part of a wider project to issue recommendations on FU protocols.

Objective: To analyse associations between RCC recurrences in patients with ccRCC, their risk group stratifications, treatments, and subsequent outcomes.

Design, setting, and participants: Nonmetastatic ccRCC patients treated with curative intent between 1 January 2006 and 31 December 2011, with at least 4 yr of FU, were included. Patient, tumour and recurrence characteristics, Leibovich score, and management and survival data were recorded. Isolated local, solitary, and oligometastatic (three or fewer lesions at a single site) recurrences were considered PC, while all others were probably incurable (PI).

Intervention: Primarily curative surgical treatment of ccRCC while at recurrence detection metastasectomy, systemic therapy, best supportive care, or observation.

Outcome measurements and statistical analysis: Incidence, time to recurrence (TTR), and OS were measured. Competing risk analysis, Kaplan-Meier, and Cox regression models were used.

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Results and limitation: Of 1265 patients with ccRCC, 286 had a recurrence, with 131 being PC and 155 PI. Five-year cumulative risks of recurrence for low- (n = 53), intermediate- (n = 105), and high-risk (n = 128) patients were, respectively, 7.2%, 23.2%, and 61.6%, of whom 52.8%, 37.1%, and 30.5% were PC, respectively. Median TTR was 25.0 for PC patients versus 17.3 mo for PI patients (p = 0.004). Median OS was longer in PC compared with that in PI patients (p < 0.001). Competing risk analysis showed highest risk of ccRCC-related death in younger and high-risk patients. Limitations were no data on comorbidities, retrospective cohort, and insufficient data excluding 12% of cohort.

Conclusions: Low-risk group recurrences are rare and develop later. Treatment of recurrences with curative intent is disappointing, especially in high-risk patients. An age- and risk score-dependent FU approach is suggested.

Patient summary: We analysed data from eight European countries, and found that the incidence of the kidney cancer recurrence and patient survival correlated with clinical factors known to predict cancer recurrence reliably and age. We conclude that these factors should be used to design follow-up strategies.

1. Introduction

Contemporary studies show that among patients with localised clear cell renal cell carcinoma (ccRCC) treated with curative intent, radical nephrectomy, or partial nephrectomy, distant or local recurrences develop within 5 yr in 20–30% of cases [1–3]. Unfortunately, recurrences are often multifocal, and with the currently available systemic therapeutic options, complete disease eradication is unlikely. However, retrospective studies and a systematic review suggest that for some of these patients, complete local treatment of limited local or distant recurrence may result in prolonged overall survival (OS) and potential cure [4,5]. Therefore, a rationale for follow-up (FU) is timely detection of potentially curable (PC) recurrences to subject them to metastasectomy or other forms of complete local treatment [6,7].

Several FU strategies based on clinicopathological characteristics (University of California, Los Angeles, Integrated Staging System; Leibovich score; and stage, size, grade, and necrosis score) are recommended for localised RCC in the major guidelines, all with comparable C-indexes for prediction of recurrence or survival [2,3,8–10]. However, the impact of FU on prolonging survival or cure was not assessed in the previous publications that had only the detection of recurrence as their main objective.

Given the poor evidence base demonstrated by a recent systematic review [11], the current study was performed under the auspices of “the euRopean association of urology renal cell carcinoma guidelines panel Collaborative multicenter consortium for the studies of follow-Up and recurrence patterns in Radically treated renal cell carcinoma patients” (RECUR). In contrast to previously published FU studies, we focused on further management after a recurrence was detected. We hypothesised that the outcome after treatment for recurrence may be dependent on risk score, symptoms at diagnosis of recurrence, age, and extent of the recurrence. For this purpose, recurrences were defined as potentially curable (PC) or probably incurable (PI) based on their extent. As a first step, the objective of the current study was to analyse associations between RCC recurrences in patients with ccRCC, their risk group stratifications, treatments, and subsequent outcomes.

2. Patients and methods

2.1. RECUR database, quality assurance, exclusions, and ethical considerations

Supplementary methods (Supplementary material) detail the RECUR inclusion and exclusion criteria, reporting of data, and statistical analyses. As of 1 May 2017, the RECUR database retrospectively collected data for 1889 consecutive nonmetastatic RCC patients from 12 centres (all with appropriate institutional approval) in eight European countries. All eligible consecutive patients underwent surgery with curative intent during the period from January 2006 (the start of the tyrosine kinase inhibitor era) to December 2011 (allowing for 4 yr of FU). All data were audited for quality and completeness by a urological surgeon (S.D.). A total of 224 (11.8%) patients were excluded due to death ≤ 90 d after primary surgery (n = 7), FU of < 4 yr (n = 111), or incomplete data (n = 106). Excluding non-ccRCC patients (n = 400), the final study population consists of 1265 ccRCC patients with a median FU of 61.9 (interquartile range [IQR] 51.9–74.2) mo.

2.2. Definitions used for analyses

Patients with ccRCC were stratified into low, intermediate, and high risk of recurrence groups according to Leibovich score [2]. Patients with recurrences were subgrouped as symptomatic or asymptomatic at the time of detection, and also subgrouped based on whether recurrence detection was within or outside of the regular FU schedule. PC recurrences were defined as isolated local, solitary distant metastatic, or oligometastatic (three or fewer lesions at a single site). All other recurrences were valued as PI, that is, more than three lesions at a single site or dissemination to two or more sites. Although not formally recognised, PC and PI were bespoke definitions chosen through consensus by the RECUR consortium, were based on a clinical utility perspective, and have been used previously [12].

2.3. Statistical analysis

A more detailed statistical analysis section is found in the Supplementary material, but in short, descriptive statistics were presented as categorical variables with percentages and continuous variables as median and IQR. For continuous and nonparametric data, independent sample t test and Mann-Whitney U tests were used, respectively. The Kaplan-Meier method with log-rank test was performed for time to recurrence (TTR) for PC and PI groups stratified by Leibovich risk score, and OS analyses between patients being symptomatic and asymptomatic at recurrence and finally between PC and PI groups stratified by Leibovich risk score. In addition, a competing risk analysis was performed
stratifying patients by Leibovich risk score and age. Where relevant, univariate Cox regression models were used to obtain hazard ratios (HRs) between groups. For all statistical comparisons, a two-tailed p value of <0.05 was considered significant. SPSS-version 24.0 (IBM Corporation, Armonk, NY, USA) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) were used.

3. Results

3.1. Recurrence patterns

Patient and tumour variables affecting ccRCC recurrence risk in the cohort of 1265 patients are shown in Table 1, while Supplementary Table 1 shows recurrence sites and clinical decision on curability in patients with recurrences and Supplementary Table 2 shows the number of imaging performed. Analysing patients with <4 yr of FU (89 with ccRCC of the 111 patients) revealed no relevant changes in FU time, recurrence rates (RRs), and TTR analyses (Supplementary Table 3). Preoperative chest computed tomography was performed in 74.6% of patients and 70% in the Leibovich low-, 65% in the intermediate-, and 83% in the high-risk group. Recurrences were found in 286 (22.6%) patients, of whom 131 (45.8%) were PC and 155 (54.2%) PI. The 5-yr cumulative RRs were 7.2% for Leibovich low- (n = 53), 23.2% for intermediate- (n = 105), and 61.6% of high-risk (n = 128) patients, of whom 52.8% (n = 28), 37.1% (n = 39), and 30.5% (n = 39) were considered PC, respectively (p < 0.001). Overall median TTR was 43.7 (IQR 25.3–59.8), 24.6 (IQR 12.8–49.3), and 12.5 (IQR 5.5–25.0) mo for low-, intermediate-, and high-risk groups, respectively (p < 0.001). Median TTR for PC recurrences was 25.0 (IQR 11.6–47.4) mo compared with 17.3 (IQR 6.2–40.3) mo for PI recurrences (p = 0.004). Cox regression analysis for TTR (Fig. 1) showed a significantly increased risk of recurrence for each incremental risk group for both PC and PI patients. In the Leibovich high-risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects</th>
<th>Events</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery (yr) (median, IQR)</td>
<td>1265 (64.1, 54.5–72.3)</td>
<td>286 (65.7, 56.8–72.6)</td>
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<td>(1.01–1.03)</td>
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<td>107</td>
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<td>1</td>
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<td></td>
<td>Right</td>
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<td>136</td>
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<td>4</td>
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<tr>
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<td>1</td>
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<td>PN</td>
<td>357</td>
<td>30</td>
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<td>Sarcomatoid component</td>
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<tr>
<td></td>
<td>Yes</td>
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<td>28</td>
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<td>(1.04–6.64)</td>
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<tr>
<td>T-stagea</td>
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<tr>
<td></td>
<td>pT1b</td>
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<td>5</td>
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<td>286 (8.0, 5.6–10.0)</td>
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<td>(1.16–1.22)</td>
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<td>1</td>
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<td></td>
<td>2</td>
<td>729</td>
<td>112</td>
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<td>(1.20–5.03)</td>
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<tr>
<td></td>
<td>3</td>
<td>321</td>
<td>109</td>
<td>6.24</td>
<td>(3.04–12.80)</td>
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<tr>
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<td>57</td>
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<td>435</td>
<td>160</td>
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<td>938</td>
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<tr>
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<td>Yes</td>
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<td>107</td>
<td>3.64</td>
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<td>256</td>
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<tr>
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<td>Yes, after PN</td>
<td>52</td>
<td>21</td>
<td>2.27</td>
<td>(1.45–3.55)</td>
</tr>
<tr>
<td></td>
<td>Yes, after PN</td>
<td>6</td>
<td>5</td>
<td>9.34</td>
<td>(3.85–22.16)</td>
</tr>
</tbody>
</table>
| CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NA = not available; PN = partial nephrectomy; RCC = renal cell carcinoma; RN = radical nephrectomy; TTR = tumour-node-metastasis.

For continuous variables “age at surgery” and “tumour size”, the HRs are estimated as per increase in years and per increase in centimetres in tumour size, respectively, while for the rest, HR estimates are categorical with first line as reference.

* TNM 2009 system.

group, the risk of having a recurrence that was PI was significantly higher (about 1.5 times) compared with a recurrence that was PC (HR 1.54, 95% confidence interval [CI] 1.08–2.21, p = 0.018). Considering all ccRCC patients with recurrences, 37.4% (n = 107) presented with symptoms and in total 29.7% (n = 85) detected outside the respective institutional FU protocols.

3.2. Management of recurrences

Figure 2 shows the distribution, curability, management, and survival outcomes of ccRCC patients developing recurrences. Curative intent treatment was offered to 79 patients with recurrence, 70 PC patients, and nine PI patients. Of the 70 PC patients, 41.5% initially had low-risk, 26.7% intermediate-risk, and 15.6% high-risk disease (Fig. 3). Of all 286 ccRCC recurrences, only 9.8% were alive with no evidence of disease (NED) at the final reported FU. However, among PC patients, 26 of 131 (19.8%) had NED at the end of FU. No significant difference was found in median TTR for PC patients with NED (n = 26) after curative intervention for recurrence (43.5 [IQR 24.6–61.4] mo) compared with those (n = 24) who experienced another recurrence after curative intervention (40.6 [IQR 15.0–55.7] mo; p = 0.313).

3.3. Survival after recurrence

Median OS after ccRCC recurrence was longer in PC patients (27.4 [IQR 11.1–48.3] mo) relative to PI patients (15.2 [IQR 5.5–33.4] mo; p < 0.001). When analysing risk score groups within PC and PI recurrences, high-risk patients with PC recurrences had significantly shorter OS compared with low-risk patients (Fig. 4A; HR 2.05; 95% CI 1.01–4.17, p = 0.046). Figure 4B illustrates that the small group of PI recurrences among low-risk ccRCC patients (n = 22) had a higher disease-related mortality rate than higher PI risk score group patients, although this was not statistically significant. Of these 22 low-risk PI recurrences, 16 (72.2%) were symptomatic at recurrence and 14 (63.7%) were detected outside the regular FU-schedule. Patients with symptomatic recurrences had significantly shorter OS than asymptomatic recurrences (HR 2.84, 95% CI 2.10–3.86, p < 0.001), independent of being PC or PI (Fig. 4C and D).

3.4. Competing risk analyses

Figure 5A illustrates that ccRCC patients’ cumulative incidence of death from other diseases exceeded the cumulative risk of recurrence in PC and PI groups at approximately 2 and 5 yr of FU, for low and intermediate risks, respectively. For high-risk patients, there was an early increase in cumulative incidence of recurrence for both PC and PI groups, which was more pronounced for PI patients. The competing cumulative risk of death from other diseases was much lower over time compared with both PC and PI recurrences in high-risk patients, of which the majority occurred within 2 yr. At approximately 2 yr of FU, the risk of death from ccRCC in the high risk score group was higher than the risk of death from other causes. Figure 5B demonstrates that for low- and intermediate-risk groups, patients > 75 yr of age had a higher risk of death from other causes than the risk of death from ccRCC recurrence. For high-risk patients, death from ccRCC recurrence was higher than death from other causes, independent of age.

4. Discussion

Recurrence patterns in ccRCC are complex, and owing to a lack of comparative studies, optimal strategies for FU have
Clear cell RCC recurrence outcome consort diagram

**Fig. 2** – Flow chart of recurrence, curability, management, and survival outcome in 1265 patients with ccRCC. Reasons for withholding therapy from potentially curable (PC) patients and type of treatment given to patients deemed as probably incurable (PI) are provided. Palliative treatment was defined as systemic therapy or best supportive care, while observation refers to refraining from active palliative treatment due to no rapid progression of disease. ccRCC = clear cell renal cell carcinoma; RCC = renal cell carcinoma.

not been established [7,13,14]. The current RECUR study showed 5-yr estimated RR for ccRCC in line with earlier reports [2,15,16]. We found PC recurrences in almost half (45.8%) of the ccRCC patients with recurrence, in keeping with previous publications [9,17–19]. In turn, approximately half of the PC patients received local treatment with curative intent of whom only 26 patients, that is, 19.8% of all patients with PC recurrences, were alive and had NED within the reported FU period. Results were not biased by excluding patients with <4 yr for FU.

The TTR did not differ between PC and PI patients in the low-risk category. This, together with a low 5-yr RR, implies that for these patients less frequent FU imaging may be considered without increasing the risk of missing a recurrence. In addition, OS after recurrence for this cohort was in line with previous publications [12,20,21]. As expected, shorter survival time was observed in the PI group, and symptomatic recurrences were significantly correlated with poorer survival. Interestingly, low-risk patients in the PI group showed a nonsignificant trend towards worse OS compared with high-risk patients. While perhaps underpowered, it is intriguing that 72.7% low-risk patients had symptoms that led to the detection of recurrence. Although this may reflect a more aggressive tumour type, this poor outcome in the low-risk group may be a consequence of very low imaging frequencies.

Competing risk analysis for all ccRCC patients revealed several differences between risk groups. For low-risk ccRCC, the analysis suggests that, together with a low cumulative RR, patients may not need frequent FU within the first 2 yr. In addition, the cumulative risk of death from other causes starts to exceed that of RR for PC and PI around the same time point. At 5 yr, there seems to be an increase in RR for both PC and PI groups, suggesting, as proposed previously, a need for continued FU after this period [11]. However, the low overall RR in low-risk patients would require a high number needed to image to identify those with symptomatic recurrences when they might still be asymptomatic, and opens up to the discussion whether general practitioner–based FU strategies may lead to comparable disease-free survival and OS as well as symptom control instead of protocols involving risk-adapted repeat imaging. Furthermore, our results suggest that FU may not be necessary for low-risk patients aged >76 yr, in line with a recent publication analysing the impact of age and comorbidity on FU [22]. For intermediate-risk patients, the RR for PC and PI
Fig. 3 – Distribution of (A) patient numbers and (B) percentages of all patients with ccRCC recurrence in Leibovich low-, intermediate-, and high-risk groups. Figure shows distribution of probably incurable recurrences and the outcomes of potentially curable recurrences. ccRCC = clear cell renal cell carcinoma; n = numbers.

seem to run parallel to the risk of death from other causes until approximately 5 yr. After 5 yr, the cumulative incidence of death from other causes exceeds the RRs, suggesting the need for age- and/or performance status–dependent FU strategy from 5 yr onwards. For the high-risk group with most recurrences, the competing risk analysis showed that death from other causes had a lower incidence than that in low- and intermediate-risk groups, reflecting the high risk of death from ccRCC in this group. Finally, as observed previously, most recurrences in high-risk patients developed within 2 yr after initial surgery [3,15–17,19,20,23,24].

Perhaps the most intriguing observation from the RECUR analysis is that FU may not have a major impact on curing recurrent ccRCC. While this is not surprising in patients with multiple recurrences, it is unexpected in patients with PC solitary or oligometastatic recurrence. Moreover, for patients with PI recurrences, observation was the management in ~25% because the extent of metastasis did not justify the start of systemic therapy, further questioning the need for intensive FU. Potentially more intensive FU among these patients (PI) may have resulted in earlier detection of recurrences and access to local treatments. However, the very early onset of recurrences in high risk patients suggests that more intensified imaging does not necessary result in better survival. Early identification of PC recurrences is a major objective of FU. However, the results of RECUR indicate that disease-free survival despite local treatment is largely unattainable in patients with recurrence from high-risk tumours (2%). At the other end of the risk spectrum, cure may be achieved in low-risk recurrences, but the low RR counters an intensive imaging FU strategy. Before recommending
any alteration to the FU strategy for ccRCC to identify curable recurrences early, one must consider that only 53% of PC recurrences were managed with local therapy, mainly metastasectomy. While this may in part be a consequence of a retrospectively assigned definition of potential resectability, this reflects real-world management, with comorbidities, poor performance, or rapid disease development arguing against local management of metastases.

Finally, a further consideration for optimising FU is the timely identification of patients with multiple recurrences who would benefit from systemic therapy. However, current systemic therapies do not cure, and placebo-controlled studies in metastatic RCC have demonstrated no inferior survival if patients crossed over into the active arm after further disease progression [25].

The strengths of this study are the large cohort and robust time-to-event analysis by excluding patients with <4 yr of FU. In addition, by excluding patients who died within 90d after surgery, we reduced potential confounding of misinterpreting primary metastatic disease as early recurrence and postoperative complications as early death. However, this study has several limitations mainly due to its retrospective nature. First, approximately 12% of patients were excluded from analysis because of a lack of essential data. Furthermore, our study did not collect data on comorbidities, that is, performance status. Patients with good performance status may have had more aggressive treatment for any recurrence, while those with poor performance status did not, thus influencing the RR and survival outcome. For planned prospective RECUR database, we therefore intend to collect these data at the time of both
Fig. 5 – (A) Competing risk analysis stratified by risk score for ccRCC patients, showing cumulative incidence for risk of recurrence in potentially curable and probably incurable patients compared with both overall risk of death from ccRCC (disease) and risk of death from other cause. Low, intermediate, and high risks of recurrence are according to Leibovich risk score. (B) Competing risk analysis stratified by risk score and age categories 18–60, 61–75, and 76–90 yr for ccRCC patients. Figure shows cumulative incidence for overall risk of death from ccRCC (disease) compared with risk of death from other cause. Low, intermediate, and high risks of recurrence are according to Leibovich risk score. ccRCC = clear cell renal cell carcinoma.
primary surgery and recurrence detection. In addition, the definitions of PC (solitary metastasis, oligometastasis with three or fewer metastases at a single site, or local recurrence) and PI (more than three metastases at a single site or disseminated disease) were based on previously published studies on local treatment and survival outcome being dependent on the number of metastases and metastatic sites [4,5], and were established by experts within the European Association of Urology Guidelines Panel for RCC. Although the definition takes the perspective of management intent at the time of diagnosis of the recurrence into consideration and has previously been published in a peer-reviewed journal [12], we acknowledge that it is not universally accepted. Finally, incidence and pattern of recurrence may have been influenced by the frequency and accuracy of imaging, which differed in the FU protocols between collaborating institutions. However, these differences are a strength of the RECUR database, which, with growing data collection, may reveal the weaknesses of certain FU strategies. While the currently collected data on frequency and type of imaging in the subgroup of patients with ccRCC recurrence (n = 286) would result in subgroups of inferior size, the future intent of the authors is to perform an in-depth analysis of these factors in a meaningful study population.

5. Conclusions

To assess the true impact of FU on survival, comprehensive data regarding the management of recurrence and its subsequent outcomes are essential; the RECUR database provides such data for ccRCC. In the low-risk group, recurrences were rare but predominantly symptomatic, which was an indicator of poorer survival outcome. Overall long-term disease-free survival following treatment of recurrences with curative intent is disappointing. This is most prominent in the Leibovich high-risk group, which harbours most patients with PC recurrences. Competing risk analysis suggests an age- and risk score–dependent approach to FU protocols, the specifics of which need further investigation. Whether regular FU pre-empts symptomatic recurrences is unproved. This and varied FU strategies need to be studied in prospective clinical trials.

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Appendix A. Supplementary data

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References


